## REMARKS

Applicants have fully considered the Non-Final Office Action of December 24, 2003. In this regard, claims 1, 3, 10, 14, 20, and 29-31 have been amended. Claims 1-14, 20, and 29-31 remain pending in the application. Reconsideration of the application is respectfully requested in view of the above amendments and the following remarks.

In the Office Action, the following objections and/or rejections were noted by the Examiner:

a. The oath or declaration was declared defective because only one of the four inventors had signed it.
b. It was noted that color photographs and drawings were submitted and that a petition must be filed and granted under 37 CFR 1.84(a)(2) to permit their use.
c. Claims 20 and 29-31 were objected to because they were dependent on non-elected claims.
d. Claims 1-14, 20, 29-31 were rejected under 35 U.S.C. § 112, first paragraph, as not complying with the enablement requirement.
e. Claim 3 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to distinctly claim the subject matter regarded as the invention.
f. Claim 20 was rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 6,060,282 in view of the prior art as exemplified by Hendrickson *et al.* and well known methods of drug design using the three dimensional structure of target protein.

The objections and/or rejections are addressed below.

### I. The procedural objections have been overcome.

#### A. The oath or declaration has been filed.

Upon further review, it appears that a declaration has been fully executed and entered into the file. In response to a "Notice to File Missing Parts of Nonprovisional Application" dated September 21, 2001, a declaration was filed on February 21, 2002 containing the signatures of the four inventors. A copy of the declaration has been attached as Exhibit A.

**B. A petition to accept color photographs and drawings has been filed.**

A petition to accept color photographs and drawings has been filed separately. A copy of the petition has been attached as Exhibit B. Additionally, please note that the specification as originally filed contains the language requested by the Examiner to be added to the specification concerning the color drawings. The language can be found on page 9, lines 22-25 of the original application.

In view of the above considerations, Applicants respectfully request withdrawal of the procedural objections.

**II. The dependent claims have been rewritten as independent claims.**

Claims 20 and 29-31 were objected to because they were dependent on non-elected claims. These claims have been amended to incorporate the parent claims. In light of the incorporation, Applicants respectfully request that the objections to claims 20 and 29-31 be withdrawn.

**III. The application enables the claimed invention.**

**A. The application conveys to the skilled artisan that the inventors had possession of the claimed invention as required by 35 U.S.C. § 112, first paragraph.**

The Examiner rejected claims 1-14, 20, and 29-31 under 35 U.S.C. § 112, first paragraph as failing to sufficiently describe the claimed invention in such terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. The Examiner stated that (1) there was no disclosure or guidance in the specification on how a skilled artisan would change the crystallization conditions with the changing of the primary structure of the single disclosed polypeptide to obtain the claimed crystals; (2) that only one crystal was described; and (3) the claims were broader than the enablement provided by the disclosure with regards to all possible crystals and complexes for any *S. pneumoniae* acyl carrier protein synthase applying the *Wands* factors. After further review, Applicants believe that sufficient disclosure has been given and respectfully traverse this rejection.

Skilled artisans are aware that the most difficult part of crystallizing any given protein is finding the optimal crystallization conditions. As the Examiner stated, knowledge regarding how to obtain any protein crystal suitable for structure determination by X-ray is lacking. Page 66, second paragraph of the application discloses those optimal crystallization conditions regarding (a) technique, (b) molecular weight, (c) temperature, (d) solution concentrations, and (e) length of time for crystallization for the claimed crystals. This disclosure would guide a skilled artisan in determining the required changes in the crystallization conditions for changes in the primary structure of the disclosed polypeptide sequence. The first full paragraph on page 34 of the application also discloses additional literature that reveals the current state of the art that would guide the skilled artisan.

Three different crystals which effectively diffract X-rays were described to show enablement, not only one as the Examiner believes. These crystals are described in Tables 3, 4, and 5.

The disclosure also enables all crystals claimed in the application. These claims are not directed to all possible crystals of any *S. pneumoniae* having any amino acid sequence. They are directed to crystals of the polypeptide sequence encoding *S. pneumoniae* acyl carrier protein synthase comprising residues 1-122 of SEQ ID NO: 1, substantially similar sequences, and their complexes. As discussed in pages 23-25 of the application, skilled artisans are aware that for a polypeptide sequence encoding a functional protein, any particular amino acid can only be substituted for by a limited set of other amino acids based on factors like hydrophobicity, hydrophilicity, charge, and size, if it is desired to retain the functionality of the protein. As stated from the last paragraph of page 21 to the end of page 22 of the specification, Applicants claim the crystals formed from those polypeptide sequences having at least 80% sequence identity with SEQ ID NO: 1 and having at least 20% of the biochemical activity of native *S. pneumoniae* acyl carrier protein synthase and their complexes.

Applicants respectfully submit that the *Wands* factors have been met. Sufficient guidance has been provided that skilled artisans would not need to experiment unduly in order to crystallize the claimed crystals. Direction and guidance have been provided through methods of identifying and purifying the synthase and through multiple working examples. As recognized by the Examiner, the state of the art is such that crystallization can be unpredictable; without such disclosure of the optimal

crystallization conditions, the success of crystallizing the claimed crystals would be greatly reduced. Taken together, the *Wands* factors favor recognition of the claims. In light of the above information, Applicants respectfully request that the rejection of claims 1-14, 20, and 29-31 be withdrawn.

The Examiner also stated that the specification did not describe a reproducible method to obtain the monoclinic crystal. However, page 66, second paragraph, shows a clear distinction between the orthorhombic and monoclinic crystals that are claimed. Crystals of native synthase are orthorhombic; crystals of the apoACP-synthase complex (listed as apo-AcpS in the specification) and of the 3',5'-ADP-AcpS complex are monoclinic. The distinction lies in whether the synthase was crystallized by itself or in complex with another molecule. Table 3 for the native synthase itself lists 2,830 atoms; Table 4 lists the apo-AcpS complex as having 2,880 atoms, and Table 5 lists the 3',5'-ADP-AcpS complex as having 2,928 atoms. Thus, the specification teaches how to make both orthorhombic and monoclinic crystals.

The Examiner stated that the specification does not teach the crystallization of SEQ ID NO: 1 itself or its selenomethionine derivative. However, page 66, second paragraph of the application teaches the crystallization of both of these sequences. The Examiner also noted that the selenomethionine derivative is an independent chemical entity and would be expected to have different physical and chemical properties from that of the wild-type sequence. However, the two sequences are *similar* in the properties relevant to protein structure and crystallization. Indeed, these similarities are the reason that substitution of selenomethionine for methionine enables the present invention. Applicants respectfully request that the rejection of claims 1-14, 20, and 29-31 be withdrawn.

**B. The application definitely claims subject matter as required by 35 U.S.C. § 112, second paragraph.**

The Examiner rejected claim 3 under 35 U.S.C. § 112, second paragraph, because the phrase "binding site shown in Figure 9" was indefinite and did not clearly set forth the boundaries of the patent protection desired. Claim 3 has been amended to remove the phrase. In light of the amendment, Applicants request that the rejection of claim 3 be withdrawn.

**IV. The invention is not obvious over the prior art as required by 35 U.S.C. § 103.**

Claim 20 was rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,060,282 (Tang, *et al.*) in view of the prior art as exemplified by Hendrickson *et al.* and well-known methods of drug design using the three-dimensional structure of the target protein. After review, Applicants traverse this rejection.

There must be some suggestion or motivation to modify or combine the references. MPEP § 2143.01. The Tang patent does not suggest that a crystal of the protein encoded by SEQ ID NO: 1 would be more desirable over the protein itself for the purpose of identifying antibacterial compounds. The Hendrickson reference, as the abstract says, "offer[s] a rather general means for the elucidation of atomic structures." EMBO J. Vol.9 no.5 pg. 1665. It does not suggest a reason to prefer crystals over proteins nor does it suggest that this particular protein should be crystallized for any reason. No clear and particular showing of an objective reason to combine references has been made sufficient to establish a *prima* facie case of obviousness.

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. MPEP § 2143.02. This burden has not been met because there has been no showing of a reasonable expectation of success in obtaining the claimed crystals with only the Tang patent and Hendrickson's method. As the Examiner has stated, the expectation of obtaining any crystal is unpredictable. However, some predictability is required to make this argument of obviousness. The prior art gives no enabling methodology for crystallizing this protein sequence and no reasonable expectation of success. *See in re Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). The Applicants have provided disclosure and guidance in obtaining the crystals for the acyl carrier protein synthase, substantially similar sequences, and their complexes that are not available in the prior art and are not obvious.

Finally, all the claim limitations must be taught or suggested by the prior art. MPEP § 2143.03. The prior art does not teach or suggest all of the claim limitations. Tang and Hendrickson do not teach that the synthase protein of SEQ ID NO: 1 can be crystallized. They do not teach the active site that binds 3'5'-ADP. They do not teach the three-dimensional arrangement of SEQ ID NO: 1. They do not teach which of the 230 possible space groups such a crystal would fall within or what the unit cell dimensions of that crystal would be. For at least the above reasons, Applicants

respectfully request that the alleged obviousness rejection of claim 20 over Tang and Hendrickson be withdrawn.

## CONCLUSION

For the reasons detailed above, it is respectfully submitted all claims remaining in the application (Claims 1-14, 20, 29-31) are now in condition for allowance. The foregoing comments do not require unnecessary additional search or examination.

In the event the Examiner considers personal contact advantageous to the disposition of this case, he/she is hereby authorized to telephone Richard M. Klein, at (216) 861-5582.

Respectfully submitted,

FAY, SHARPE, FAGAN,
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June 21, 2004
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